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VIROLOGIC AND CLINICAL OUTCOMES OF HEPATITIS B VIRUS INFECTION IN RECIPIENTS UNDERGOING UNRELATED-DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introdution: Hepatitis B virus (HBV) infection in recipients may be associated with hepatitis and increased nonrelapse mortality (NRM) following unrelated-donor allogeneic hematopoietic stem cell transplantation (allo-HSCT). China is an endemic area for HBV infection. It is especially significant to clarify the true impact of HBV on outcomes of allo-HSCT as well as preventive and treatment strategies in this special population. In the current study, we performed a retrospective analysis of the virologic and clinical outcomes of HBV infection in recipients undergoing allo-HSCT with active anti-HBV prophylaxis or treatment from seronegative unrelated donors for HBV.

Patients and Methods: Between 1998 and May 2009, 222 patients underwent unrelated donor allo-HSCT were enrolled. Patient information was collected from the BMT database. Anti-HBV therapy consisted of lamivudine or entecavir for HBsAg positive recipients before HSCT while marrow harvest and HSCT were performed until recipient's serum HBV-DNA became undetectable. HBV-DNA was isolated from serum with the QIAmpt blood kit and quantitatively measured using a kinetic fluorescence detection system. All of the patients were followed up in out-patient department weekly and HBV serology were detected once every month.

Results: Before transplantation, 17 patients who were positive for HBsAg and received lamivudine or entecavir prophylaxis were regarded as group 1. There was 1 case of reactivation of HBV in this group and 8 cases became negative for HBsAg and posive for HBsAb. One hundred and fifty four patients who were negative for HBsAg and anti-HBc before allo-HSCT were regarded as a control group. Fifty one patients who were negative for HBsAg and positive for anti-HBc were regarded as group 2. In the control group none was identified as positive for HBsAg after HSCT while in group 2, 2 patients developed hepatitis, thus indicating reverse seroconversion. For these 2 patients lamivudine were administered for anti-HBV therapy and 1 patients died of HBV-related hepatic failure. There were no significant differences in overall survival(OS), and incidence of acute graft-versus-host disease(GVHD) and chronic GVHD among the 3 groups.

Conclusion: Our data suggest that HBV infection in the recipient at the time of transplantation does not seem to adversely affect outcome after allo-HSCT with active anti-HBV prophylaxis or treatment. HBV infection in the recipient is not a contraindication of allo-HSCT.

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FLAGELLIN REDUCES GVHD THROUGH EARLY IMMUNOSUPPRESSION INDUCED BY THE FLAGELLIN-TLR5 IMMUNE INTERACTION OF HOST CELLS IN ALLOGENEIC HSCT RECIPIENTS

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We previously showed that flagellin (Fla) significantly reduced GvHD in H-2^K→ H-2^b HSCT model and had better long-term survival. Here, we reported the mechanisms by which Fla reduces GvHD using similar HSCT model and also B6 BM → B6TLR5 knock out (KO) and KO BM →B6 radiation chimeras. We hypothesized that flagellin-TLR5 binding in the host gut epithelium will be responsible to reduce GvHD. To determine the flagellin effects on early days of transplant, Fla-treated (50-µg/mouse i.p 3 hrs before irradiation and 24 hrs after transplant) B6 recipients of $3x10^6$ splenocytes and $5x10^6$ TCD BM cells from H-2^K donors were sacrificed on day 4 and 10 after post transplant. Splenocytes were analyzed by FACS. Fla-treated recipients had significantly lower numbers of cells per spleen compared to controls [p = 0.002] on day 4 post transplant but not on day 10 [p = 0.43] post-transplant. Accordingly, the numbers of donor spleen-derived CD4 and CD8 T cells per spleen in Fla-treated recipients were significantly lower compared to PBS-treated recipients on day 4 post transplant. The early activation status of donor T cells in the spleen of Fl-treated recipients was also found significantly lower compared to controls. Next, we addressed our hypothesis by doing similar experiments using radiation chimeras. Radiation chimeras were generated by transplanting $10x10^6$ BM cells from B6 and/or KO donors to 11Gy irradiated B6 or KO recipients. B6→KO, KO→B6, B6→B6, KO→KO radiation chimeras were again irradiated with 9.0Gy and transplanted with $3x10^6$ H-2^K splenocytes and 5 x 10^6TCD BM 12 weeks later. Each group received two doses of Fla or PBS i.p. Survival and weight loss were determined. Fla-treated B6→B6 radiation chimeras (TLR5+ donor and host hematopoietic and host epithelial cells) survived 100% with only mild GvHD (12% weight loss at day 79 post transplant). 50% of Fla-treated B6→KO (TLR5+ donor hematopoietic cells) and 40% of KO→ B6 (TLR5+ host hematopoietic and epithelial cells) chimeras survived with 15% and 18% weight loss, respectively. All the Fla-treated KO→ KO recipients died within 65 days post transplant. On the other hand, all 4 groups of PBS-treated control recipients died or were sacrificed due to GvHD-associated weight loss exceeding 25%.

Conclusion: Flagellin reduces GvHD by suppressing the activities of donor T cells within 4 days post-transplant. The early immunosuppression may be the result of Fla-TLR5 immune interaction in the host epithelium that reduces GvHD.

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USE OF RABBIT ANTI-THYMOCYTE GLOBULIN FOR CONDITIONING IN MATCHED UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION PROVIDES COMPARABLE DOSE DEPENDANT OUTCOMES TO MATCHED RELATED DONOR RECIPIENTS

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Rabbit Anti-thymocyte globulin (ATG) is used as prophylaxis against graft vs. host disease (GVHD) following allogeneic hematopoietic cell transplant (HCT). At our institution ATG (7.5 or 10 mg/kg infused over three days from day -3 to day -1) is used in the conditioning of matched unrelated donor (MUD) transplant recipients but not in matched related donor (MRD) recipients. We retrospectively studied post transplant outcomes between MUD and MRD recipients with acute leukemias or myelodysplasia to study the impact ATG might have on post transplant outcomes. Patients transplanted between 2004 and 2009 were included in the study (n = 98). Fifty patients underwent MUD HCT and received ATG (ATG group); 48 in the MRD group did not receive ATG (no ATG group). There were no significant differences between the groups in day 100 mortality (RR 0.57, 95% CI 0.23, 1.4; P = 0.24), acute GVHD (aGVHD) (RR 1.74; 95% CI 0.9, 3.2; P = 0.07), or relapse (RR 1.07; 95% CI 0.45, 2.39; P = 0.87). Chronic GVHD (cGVHD) incidence was significantly lower in the ATG group when compared with the no ATG group (RR 0.22, 95% CI 0.09-0.58; P = 0.0018). At a median follow up of 36 months in the entire cohort, 50% patients are alive in the ATG group with a median survival of 36 months, and 63% of the patients are alive in the no ATG group (Log Rank P = 0.13). The 2-year survival for the ATG vs. no ATG cohorts is 51% (95% CI, 30%, 72%) vs. 63% (95% CI, 38%, 82%) (Log-Rank P = 0.2145). To further explore the effect of ATG dose on post transplant outcomes, patients who received 10 mg/kg dose of ATG (52% of ATG recipients) were compared to those who received 7.5 mg/kg. Relapse rate, as well as acute and chronic GVHD rate was comparable in the two groups, however all cause mortality in the 10 mg/kg ATG dose group was significantly higher (RR 0.54, 95% CI 0.3, 0.96; P = 0.03) mostly due to infections. We conclude that the addition of ATG to the conditioning regimen of patients undergoing MUD HCT reduces the risk of developing chronic GVHD, resulting in overall survival rates which are comparable to MRD HCT recipients. Outcomes were superior when an ATG dose of 7.5 mg/kg was used in our patients. We submit that ATG use in conditioning MUD HCT recipients will yield benefit beyond recently adopted standards of stringent HLA matching and improved supportive care.